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Methodology Series Module 4: Clinical Trials

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Abstract

In a clinical trial, study participants are (usually) divided into two groups. One group is then given the intervention and the other group is not given the intervention (or may be given some existing standard of care). We compare the outcomes in these groups and assess the role of intervention. Some of the trial designs are (1) parallel study design, (2) cross-over design, (3) factorial design, and (4) withdrawal group design. The trials can also be classified according to the stage of the trial (Phase I, II, III, and IV) or the nature of the trial (efficacy vs. effectiveness trials, superiority vs. equivalence trials). Randomization is one of the procedures by which we allocate different interventions to the groups. It ensures that all the included participants have a specified probability of being allocated to either of the groups in the intervention study. If participants and the investigator know about the allocation of the intervention, then it is called an "open trial." However, many of the trials are not open – they are blinded. Blinding is useful to minimize bias in clinical trials. The researcher should familiarize themselves with the CONSORT statement and the appropriate Clinical Trials Registry of India.

Key Words: *Blinding, clinical trials, design, randomisation*

Introduction

In the past three sections, we have discussed some aspects of observational studies. If the readers remember, in observational studies, the researcher merely observes the exposure and the outcome. There is no modification or allocation of the exposure by the researcher. If, however, the researcher allocates or modifies the exposure, then it is called an interventional study also called experimental study. Evaluation on new drug or device or procedure in human subjects. We will be discussing the randomized controlled trials (RCTs) in this part of the methodology module.

The definition of an RCT is "*a clinic-epidemiological experiment in which subjects are randomly allocated into group, usually called the test and control groups, to receive or not a preventive of a therapeutic procedure or an intervention*" (Porta, 2014).

Since these studies are done prospectively and the intervention is allocated by the investigator, this type of study provides a high level of evidence and often considered a gold standard. In the hierarchy of evidence, RCTs have been placed above the case reports and case series, other types of observational study designs (cross-sectional, case–control, and cohort), and just below systematic reviews and meta-analysis. A well-designed, executed, and analyzed RCT can provide a high quality of evidence for the usefulness of interventions in the population. It should be remembered that RCTs are experimental epidemiological studies conducted on human participants. Thus, ethics form an important component of the design of these studies (it should be remembered that ethics are important for any study that involves human participants). We will discuss ethics in experimental studies in greater detail subsequently in this manuscript.

This design can be used to answer various types of research questions. Some types of research questions in RCTs are (1) comparison of different types of drugs in the treatment of a condition (compare doxycycline and azithromycin in the treatment of bacterial infections), (2) comparison of different doses of the

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same drug (single higher dose of azithromycin vs. 5 days of regular dose of azithromycin in the treatment of bacterial infections), (3) comparison of two different types of formulations of the same medication (cream vs. ointment for treatment of eczemas), (4) comparison of two different methods of treatment (surgery vs. oral medications in treatment of vitiligo), and (5) comparison of behavioral interventions or procedures. These are just some examples of potential research questions. We will also discuss other types of trials in this manuscript.

Design

In a clinical trial, study participants are (usually) divided into two groups. One group is then given the intervention and the other group is not given the intervention (or may be given some existing standard of care). The intervention is (usually) assigned randomly. They are then followed over time to assess the change in the outcomes in both the groups. We compare the outcomes in these groups and assess the role of intervention. Even though in a clinical trial, participants are followed up prospectively (often more than once), the design is not called a "cohort study."

Examples of Randomized Controlled Clinical Trials

Effectiveness and safety of clofazimine and pentoxifylline (Roy et al., 2015)

Roy and colleagues conducted a double-blind RCT to compare the effectiveness and safety in the treatment of Type 2 lepra reactions. They recruited twenty participants and divided into two groups: One group received pentoxifylline 400 mg TDS + prednisolone (40 mg daily tapered over 12 weeks) and the second group received clofazimine 100 mg TDS + prednisolone (40 mg daily tapered over 12 weeks). They assessed the number of days required for complete remission of skin lesion and systemic symptoms.

They found that the clofazimine group showed a longer time for resolution; however, the total number of days required for complete remission in both the groups was similar. They concluded that both pentoxifylline and clofazimine reduced the cutaneous and systemic symptoms similarly. However, the former reduced initial severity, whereas the latter provided sustained improvement and acted slowly.

Study of treatments for pyoderma gangrenosum patients randomized controlled trial (Ormerod et al., 2015)

The group presented the results of a trial comparing cyclosporine and prednisolone in the treatment of pyoderma gangrenosum. It was a multicenter, parallel group, RCT. They recruited 121 patients from 39 hospitals in the United Kingdom. Of these, 59 patients were given 4 mg/kg/day of cyclosporine (maximum of 400 mg/day) and 53 patients were given 0.75 mg/kg/day of prednisolone (maximum of 75 mg/day).

They assessed healing over a period of 6 weeks. This outcome was assessed by digital cameras and blinded investigators. Thus, the authors have described this trial as observer blinded. The investigators also evaluated the time to healing, global treatment response, self-reported pain, and quality of life (these were described as secondary outcomes). They found no difference in prednisolone and cyclosporine across these multiple outcomes. Hence, they concluded that treatment decisions may be based on side effect profiles and patient preferences.

These are two examples of RCTs. We encourage the readers to read these studies completely to understand practical aspects of design and analysis of RCTs.

Types of Randomized Controlled Trials

We will discuss the various types of trial designs. The four important types of designs have been described in Table 1.

The trials can also be classified in some other different ways.

Phases of clinical trial (for new drug)

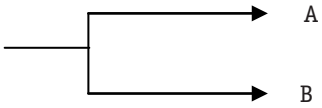
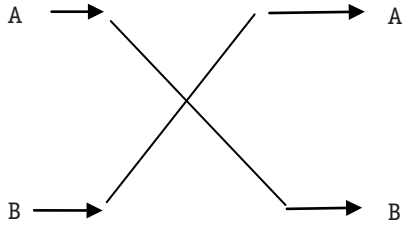
i. Phase I trials
   - Conducted after animal studies
   - May be conducted in healthy volunteers or in individuals who have the disease with no known existing cure
   - Looks at pharmacokinetics and pharmacodynamics of the drug. Used for the assessment of safety, particularly immediate short-term safety at higher dosage
   - They are usually neither randomized nor controlled.

ii. Phase II trials
   - Conducted among a small group of patients
   - Assesses the efficacy and provides additional information on safety of the drug
   - Can be used to evaluate various doses and frequency of administration.

iii. Phase III trials
   - Conducted after the efficacy and safety trials
   - Conducted to evaluate the effectiveness of the study
   - Mostly conducted as RCTs.

iv. Phase IV trials
   - After the drug has been approved and marketed
   - Postmarketing surveys
   - Monitor the side effects after marketing.

Table 1: Different types of designs

Type	Method	Additional points	Figure
Parallel group design	In this design, there are two groups: one group is given the intervention and the other group acts as the control group	This is one of the most common forms of designs used. The two examples provided earlier are examples of parallel group design Sometimes, you may have more than two groups in the trial Although in general the interventions are allocated randomly to each of the groups, sometimes the allocation may be nonrandom	
Cross-over design	In this design, the participants are given both the interventions; the participants in the study act as their own controls The participants are randomized into two groups. one group receives intervention A and other group receives intervention B (or placebo). Once the entire duration of the treatment is over for the first part, there is a period when none of the interventions are administered - this is called the washout period After the washout period is over, the interventions are switched Thus, if one participant received intervention A before the washout period, the same participant received intervention B after the washout period	It is important that intervention in the first part of the trial does not carry over to the second par - thus, the washout period should be adequate It is also important that the condition is relatively stable and does not get completely cured in the first part of the trial (otherwise we will not be able to use the intervention after the washout period) It is a useful design since we are comparing both the interventions in the same participant - within participant difference	
Factorial design	Here, the investigators test more than one intervention simultaneously. One group received both the interventions. One group receives the first intervention. One group receives the second intervention. And one group is the control (standard treatment or placebo)	This is useful because we can test both interventions at the same time. The same group of controls can be used for comparison Sometimes, the factorial designs many be more complex	Testing interventions A and B Group 1: Both A and B Group 2: A Group 3: B Group 4: Control
Withdrawal group design	In this type of design - interventions for chronic diseases are stopped or dosage reduced	These designs are useful for the evaluation of duration of the treatment in chronic diseases It may also be useful to assess the interventions without any conclusive evidence in the literature	

Nature of the clinical trial: Efficacy versus effectiveness

i. Efficacy trials
- Evaluates whether an intervention works in the population that actually receive it
- Usually conducted in a homogenous group of individuals
- These are explanatory trials
- The trials are conducted in controlled conditions and outcomes are supposed to be as clean as possible
- These are usually proof of concept studies conducted in a highly selected group of individuals who have the disease. We may have very strict inclusion criteria for these types of studies. The Phase II studies may be considered efficacy studies
- For example, Babino *et al*. conducted an open-label study to assess the efficacy of a topical medication containing 0.8% piroxicam and sunscreen in the treatment of actinic keratosis. They conducted this trial as a proof of concept study – the rationale for the study being that since cyclooxygenase 1 and 2 enzymes are upregulated in actinic keratoses, application of an enzyme inhibitor may be useful in this condition

- It is important to maintain strict control in such studies. For instance, in the above-mentioned study, the participants should not have applied or used any other medication. Furthermore, the participants should have followed the instructions completely (used the amount of medication as instructed, number of applications should be as per instruction, etc.).

ii. Effectiveness trials
- Evaluates whether an intervention works in that it intended to be used
- These are pragmatic trials
- The trial is conducted in real-life clinical scenarios
- The exclusion criteria may not be as stringent as in efficacy studies; they tend to be more pragmatic
- The study participants are observed in a more real world scenario some of them may miss their medications, some may apply more than required, or some may use other products simultaneously. Although we would like to avoid such scenarios, these cannot be completely ruled out in real life situations
- Many of the RCTs conducted by investigators tend to be effectiveness studies. For example, we may compare methotrexate and prednisolone for the treatment of psoriasis in our outpatient department. This can be in the form of an RCT. We will monitor the study participants over a period of 1-year. During this time, it is possible that many participants may miss their dose, or may apply other products on their lesion. This may influence the results. Hence, it is important to note these points in follow-up and account for them in the analysis.

Type of clinical trial

i. Superiority trials
- Common type of RCTs
- These studies assess if one intervention is different compared with existing intervention or a placebo. Usually, we are interested to show that the new intervention is better than the standard one or the placebo
- The null hypothesis in this study is that there is no difference between the two interventions
- The alternative hypothesis is there is a difference between the two interventions or new intervention is better than the standard one. The former is a nondirectional alternative and the latter is a directional alternative.

ii. Equivalence trials
- However, we are not always interested in showing that the new intervention is better than the existing one. We may only be interested in showing that the new intervention is equivalent to the existing one. However, the new intervention may be cost-effective or less toxic compared with the existing one
- The null hypothesis in this type of trial is that the difference between the new intervention and the standard intervention is greater than AAAA units in either direction (lower or higher). You have to carefully look at the literature to decide the value for this difference. The equivalence value has to be set for the null hypothesis so that this amount is considered clinically insignificant
- The alternative hypothesis in equivalence trials is that difference between the new intervention and the standard intervention is not greater than AAAA units in either direction (higher or lower).

iii. Noninferiority trials
- Sometimes, we may be interested in showing that the new intervention is "not worse" compared with the existing intervention
- However, the new intervention may be less harmful or toxic
- Such types of trials are called noninferiority trials
- It may be used in conditions when the new intervention is relatively easier to use or may be less toxic
- In such a trial, the null hypothesis will be that difference between the standard intervention and the new intervention is greater by AAAA units (in one direction). The alternate hypothesis will be that the difference is less by AAAA units.

Some Important Aspects of Clinical Trials

Randomization

It is one of the procedures by which we allocate the interventions to different groups. Randomization ensures that all the included participants have a specified probability of being allocated to either of the groups in the intervention study.

Randomization ensures that the known and particularly unknown variables are equally distributed across both groups. However, it has been highlighted that even after randomization the groups may not be similar. Thus, it is still important to compare the intervention groups at baseline in your analysis (you may want to account for some of the observed differences – if any in your analysis). By randomization, we also ensure that the allocation into different groups is not dependent on the investigator.

How do I randomize?

Well, a flip of a coin is a random event. The researcher may decide: Heads – participant is given intervention A and tails – participant is given intervention B. What if all the initial coin flips are heads? You will not have

patients in the Group B. This is a practical difficulty of using a coin.

Hence, you may use other methods for randomization. You may use random number tables, random table generators, and computer programs for randomization. The tables may become complicated if there are more than two groups (e.g., in a factorial design). Hence, it is best to consult with a statistician before proceeding with randomization.

Can I use the date of birth or day of admission/presentation for randomization? These are not true randomization procedures. Some may call as being it as "pseudo-random" or "quasi-random."

We have described some types of randomization procedures in Table 2.

Please note that the researcher has to state the method of randomization explicitly in the protocol, as well as the publication.

Blinding

If the participants and the investigator know about the allocation of the intervention, then it is called an "open trial."

However, many of the trials are not open – they are blinded. Blinding is useful to minimize bias in clinical trials. The investigator may blind the allocation of intervention, assessment of individuals, or data analysis. The various types of blinding were as follows:

Single-blinded trials

In this type of trial, the patients are blinded to the intervention. However, the investigators know about the intervention given to the participants. The main disadvantage is with this design is that bias due to investigator evaluation and assessment will not be avoided in this type of design.

Double-blinded trials

Many of the RCTs are double-blinded trials. In such a design, neither the investigator nor the participants know about the intervention allocation to the participants. This type of blinding reduces the biases due to assessment and evaluation by the investigators. For example, if the trial is not double blinded then the investigator knows the intervention allocated to each participant. If the investigator is biased toward one particular intervention, then she/he is more likely to report favorable outcomes for that particular intervention compared with the other intervention. Double-blinding tries to minimize this bias.

How do I achieve double blinding?

It is important to understand the process of double blinding. If the medication is compared with the placebo, then both have to be similar (appearance, etc.). The intervention and the placebo should be placed in similar boxes. These boxes should be prepared by an individual who is not a part of the investigating team (such as the central pharmacist). This person will receive the two interventions, divide them into two groups and label them in similar boxes/envelopes/blister packs (individual codes). These code-labeled boxes will then be given to the investigator who will then dispense these to the participants. Only the central pharmacist/person who has generated the randomization will know about the link between the codes and the intervention provided

Table 2: Types of randomization

Simple randomization	It is one of the basic forms of randomization. All the participants are randomized in groups based on random tables or computer-generated random number list
	A problem with this type of approach is that if for any reason the trial is stopped midway, the groups may be unequally balanced
	For example, we have to randomize thirty individuals into two treatments (A and B). We have used computer-generated random number list. It just so happens that the first seven were randomized to Group A, and the eight individual was randomized to Group B. If for some reason, we cannot continue the study further, we will have very unequal groups (7 in Group A and 1 in Group B). Thus, this information may not be useful. We can avoid this by using other methods of randomization
Blocked randomization	In this, the entire study population is divided into blocks (or subgroups). They are usually divided into blocks of even numbers, for example, 4, 6, or 8. The participants are then divided into intervention A and B in these blocks
	For example, if we had to randomize forty people into two groups (Group A and B). We will divide these forty people in ten blocks of four each. The participants are randomized into Group A and B within each block. Thus, after every four recruitments, we will have two individuals each in Group A and B. Hence, even if the study stops midway (for any reason), both the groups will tend to have equal number of participants
Stratified randomization	Sometimes, the participants are divided into various strata and they are then randomized within the strata. For example, the total population can be divided into two groups based on their sex (male/female). Within each strata, the population can be randomized into two groups
	You may use block randomization method within the strata

to each participant in the group. Such a procedure is also termed as "allocation concealment." By this concealment, the individuals dispensing the boxes to the participants will not know the randomization sequence, the medication in the box, and which medication is being given to each participant.

In the above -mentioned example (pentoxifylline and clofazimine study), the authors inserted both the medications in similar looking gelatin capsules. These capsules were then placed in identical looking boxes. Thus, even if the investigator opened the boxes, the capsules would look identical; they will be blinded to the content of the intervention.

Triple blinding

In this, you can blind the evaluators or assessors. Sometimes the data analyst may also be blinded to the two groups. The data are just presented as Group A and B; the type interventions are stated only after data have been analyzed.

Sometimes, it may be necessary to unblind the interventions. This may be if there a serious adverse event or if required by the data safety monitoring board.

Placebo-controlled studies

A placebo is usually an inert substance that is given to some participants in a study arm in RCT. Usually, the physical properties of the placebo are similar to the active intervention under study (for example, same color, consistency, and taste). Thus, the participant who receives the placebo is unable to judge whether the intervention administered is the active ingredient or a placebo. These studies are called placebo-controlled studies. Usually, efficacy trials are placebo-controlled studies. However, many effectiveness studies are also placebo-controlled studies.

Should we do a placebo-controlled study? When should we do placebo-controlled studies?

This issue needs to be tackled at multiple levels. A general rule is that the study participant cannot be denied the existing standard of care. So for instance, if there is known standard treatment for acne, an investigator will not be allowed to conduct a study comparing doxycycline versus placebo in acne patients. Nonetheless, some regulatory trials may require comparison with a placebo. In such a scenario, the study participant should be aware that is possible that she/he may be randomized to a placebo group. The consent document should clearly mention that "there is a 50% probability that you may be randomized to either the study group or the placebo group. The study medication contains XXXYY and the placebo will be a similar looking medication without any active ingredient. Neither you nor the investigator will know the group as well as the medication you have received."

Placebo trials have always been an issue of ethical debate. Should they be done? In fact, one can also extend the argument: Should RCTs be done at all? Is it ethical as a researcher/investigator to conduct a trial? We will discuss these issues in the next few paragraphs.

Ethics of clinical trials

As briefly discussed earlier, ethics form an important part of clinical research, particularly clinical trials. Should researchers be allowed to conduct any trial for science? Historically, a lot of studied have been conducted that would consider completely unethical. In fact, some of these have also been funded by government bodies. One such study called the Tuskegee Syphilis Study was funded by the United States Public Health Services. This was conducted to study the natural history of syphilis among African-American patients. The participants were denied the treatment (penicillin) even when there was evidence that this treatment is useful for the management of syphilis. The trial had many long lasting impacts – many communities were skeptical of participation in clinical trials. Indeed, the President of the United States apologized for the conduct of this study.

Although with greater emphasis of ethics in research, it is quite likely that such a study will not be allowed to be conducted by Ethics Committees, the onus of ethics is as much on the researcher as it is on the members of the Ethics Committees. If there is published meta-analysis in a peer-reviewed journal on the role of the intervention, the researcher cannot design a trial without a reference to this meta-analysis. The rationale should be based on the findings of this meta-analysis. For example, if there is a meta-analysis which conclusively states that prednisolone is better in psoriasis compared with methotrexate, the investigators cannot design an RCT to compare the effectiveness of prednisolone and methotrexate in psoriasis patients. A golden rule is that study participants cannot be denied the existing standard of care.

At this point, let us introduce a new term - "equipoise." Jadad and Enkin (2007) have discussed this extensively in their book. It essentially means that an investigator does not know which treatment will be useful for the condition; the investigator just allows each intervention to take its own course. The importance of individual-level equipoise is that if the researcher knows that intervention A is better than intervention B, then a trial comparing interventions A and B may be considered unethical. Furthermore, there is also a concept of "collective equipoise" – there is genuinely no agreement among the research/clinical community as to what is the standard of care or which is a better therapy. Such situations demand well-designed and conducted clinical trials; thus, RCTs may be ethical in these scenarios.

Another important ethical point is should trials be conducted in populations who cannot afford the medications or for whom the medications will not be available? The Ethics Committee may ask questions about continuity of medication after the completion of the trial. The investigators should be aware of these while designing the trial.

Informed consent and assent

The Indian Council for Medical Research has published a document on Ethical Guidelines for Biomedical Research on Human Participants. The readers are encouraged to read the complete document to understand the rules and regulations in India.

The "informed consent" document is an important component of the RCT. The informed consent document should cover these important areas: (1) Detail of investigators, (2) detail of the study (sponsor etc.), (3) details about the duration of participation (including the number of visits) and the procedures that will be done at each visit, (4) detail of the intervention products, and (5) if the participant will be randomized. It should be clearly stated in the consent form that "the participant will be randomized to either of the interventions (or a placebo if it is a placebo-controlled trial)," (6) mention about blinding, (7) alternative treatment available, (8) benefits of participation, (9) risks about participation, (10) compensation to the participants (monetary or other) for participation in the study, (11) compensation in case of trial related injury, (12) right to refuse participation in the trial (without any consequences now or in future), (13) contact information of the investigator and a representative of the Ethics Committee, (14) any other information that is required by the trial or the committee. The consent form should be in simple language and in a language that is understood by the participant.

Another important document is called the "assent." This is obtained from "children" who are the participants in a study trial. If a child from the age of 7 to 18 is recruited in the study, then in addition to the consent by the parents/guardian, the investigators should get an assent from the child.

In India, the guidelines state that informed consent procedures for a clinical trial should also be required audio-visually. These records along with the other consent documents should also be preserved. In case of anti-HIV and antileprosy clinical trials, the investigators should only audio-record the consent procedure; they need not record the procedure visually. Furthermore, the consent document should not be in technical language; it should be in simple language that can be understood by the participants. If the individual is unable to read the consent form, there should be an independent witness during the entire consent procedure. This independent witness should also sign the consent document.

Sample size and patient selection

For any RCT, the sample size should be calculated "*a priori*" with sufficient justification. Although the statistical details of sample size calculation will be elaborated in the biostatistics module, we will discuss certain important concepts here.

The sample size calculation will depend on the outcome of interest (continuous, proportion, etc.). Since usually the RCTs are two group studies, the sample size will be estimated using formulae for two independent means or proportions (other formulae may also be used for other outcomes, e.g., survival). However, while estimating the sample size, we also have to account for refusal at the time of entry and losses to follow-up. For instance, you have estimated (based on effect size, alpha, and power) a sample size of 56 participants in the intervention and the control arm. Since RCTs are usually follow-up studies, some of the participants may not complete the entire procedure. They will be considered as "lost to follow-up." We have to account for this in the sample size. For example, if we expect 10% data loss (based on the previous experience or studies in similar settings), we should inflate the sample size by this number. Thus, the final sample size should be 61 is each group. One may also add the refusal for participation to the sample size. For instance, if one expects 20% refusal for participation, then the sample size should also be inflated by 20%. Thus, the total number of participants that have to be approached will be 146 (73 for each group). This calculation should be explained in the methods section of the protocol and the manuscript.

If one is not able to recruit the required number of patients, it should be explicitly stated in the methods section of the manuscript. In this case, it will be useful to do power calculation (since the sample size was calculated based on the effect size that we had initially intended). This power should be stated in the analysis section.

Patient selection

It is important to recruit the appropriate participants for the study. At this point, it will be important to understand the difference between "random selection or participants" and "random allocation of interventions." By random selection, one will recruit participants in the study based on a predetermined random selection pattern. However, one may recruit all consecutive participants for an RCT (based on inclusion and exclusion criteria). They will, however, be allocated randomly, either to the intervention group or the control group – this is random allocation.

One should avoid "selection bias" while recruiting participants for the study or while allocating the study

participants. The inclusion and exclusion criteria should be adhered to strictly. Similarly, the randomization schedule should be clearly defined and adhered to strictly during the entire duration of the study. For example, if the inclusion criterion is acne Grade II and above (and acne scars are not included in the exclusion criteria), one should not arbitrarily exclude a patient with many acne scars, just because one feels that the drug may not work in this patient. If scars are important for the drug mechanism, then it should be mentioned "*a priori*" in the protocol. The investigator cannot and should not decide whom to include and whom to exclude.

If the number of participants are large and cannot be recruited, then the investigator may recruit these from multiple centers. However, the protocol to recruit the participants should be similar across all the centers.

Protocol for randomized controlled trials

The protocol for RCTs is usually similar to other study designs. Some of the important components of the study protocol should include (1) background and rationale for the trial (include any systematic review or meta-analysis in the background), (2) objectives of the trial (primary objective and additional secondary objectives – if any), (3) study population (recruitment procedures and inclusion and exclusion criteria), (4) sample size of the study (including the calculation and justification), (5) design of the trial (single arm study, parallel design, cross-over, etc.), randomization, and blinding procedures, (6) follow-up visits (nature and frequency), (7) measurement of baseline parameters and variables during the follow-up visits, (8) data analysis including interim analysis, (9) early termination of the trial (if desired), and (10) ethics of the trail (consent form etc.).

Although these are some of the important components of a protocol, the investigators should also include the timeline for the study, the organization of trial (including individuals responsible for recruitment of participants, randomization, blinding, allocating the intervention, observing the outcomes, etc.), and any additional documents (data collection forms and questionnaires).

It is important to note that the study protocol should be followed as written in the document. If there are any changes to the protocol, then the reasons for the change should be documented and should also be mentioned in the manuscript. The changes cannot be done arbitrarily and should be adequately justified.

Analysis of Data

The analysis of data will be based on the nature of the outcomes. For example, one may estimate the total proportion of individuals with the favorable outcome in intervention A compared with intervention B. The investigator may estimate the odds ratios or mean difference (in case of continuous outcomes). The reader is encouraged to refer to the biostatistics module for a comprehensive description of the data analysis methods.

In many intervention trials, participants are required to follow-up multiple times. The outcomes are measured over time. What if some participants do not complete the intervention? They are "losses" in the trial. They are considered "lost-to-follow-up." In this age of communication, one may call up as ask them the reason. However, we may never know the real reason for their not turning up. Some of the potential reasons are moved to some other place of residence, they improved and did not feel the need to follow-up, or they worsened or did not lead to follow-up. If you exclude these patients from the analysis, then the results may be biased. Thus, it is argued that we include all the patients according to the way they have been randomized. Their group should not be changed even if there is a deviation from the original protocol. This is called "intention-to-treat" analysis.

The other form of analysis is when we include only those who individuals who received the intervention after randomization and adhered to the protocol be included for analysis. This is called per-protocol analysis. As discussed earlier, a bias may be introduced if we only conduct per-protocol analysis. Furthermore, we may lose a lot of participants for noncompliance; this may reduce the power of the study.

Interim analysis and early stopping of trials

Sometimes, it may be necessary to stop the trial mid-way. If one intervention is so much better or worse compared with the other intervention, it may be unethical to continue the trial. However, this cannot be done arbitrarily and the procedure to do this must be incorporated in the protocol. The investigator should explicitly state – when will the interim analyses be done? What boundaries will be used for early stopping?

There are some specific statistical guidelines for stopping the trials early; some of these methods are quite advanced. Hence, the investigator should consult a statistician and incorporate these methods in the protocol.

An RCT to study the effect of male circumcision was conducted in the South Africa (Auvert *et al.*, 2005). In this trial, the investigators had included interim analyses in the protocol. During the interim analysis, they found that the intervention was very protective with a *P* value which was below the threshold value (as included in the protocol). Hence, if the investigators would like to conduct interim analysis, it should be well thought through in consultation with a statistician.

Additional Points

CONSORT statement

CONSORT is Consolidated Standards of Reporting Trials. The group has developed guidelines to report RCTs in the literature. It has a checklist of 25 items (title, abstract, introduction, methods, results, discussion, registration, protocol, and funding) and a flow diagram. Since most of the journals want the authors to submit RCTs along with the CONSORT checklist and flow diagram, we strongly encourage the readers to familiarize themselves with CONSORT (http://www.consort-statement.org/). In fact, the CONSORT statement has also been extended to noninferiority and equivalence trials.

Clinical Trials Registry - India

All the researchers who wish to conduct RCTs should register their trials in a registry. In India, this registry is called the Clinical Trials Registry – India. This registry is hosted by the National Institute of Medical Statistics. The Drugs Controller General (India) has made trial registration mandatory and most journals would require a registry number for publication. Thus, it is important that researchers become familiar with the requirements of the registry (http://ctri.nic.in/clinicaltrials/login.php).

Schedule Y and Good Clinical Practice guidelines

The clinical trials for import of new drugs, manufacture of new drugs, and sale of existing drugs for other indications are controlled by the Drugs and Cosmetics Rules (1945) under its Schedule Y. We have provided a link to the document in the bibliography. The document outlines the procedures to be followed by the sponsors of trials and the investigators during the conduct of the trial. The document also highlights the ethical procedures, role of the Ethics Committees, and the application details have also been described in this document. All the investigators should read the document and if the trial they are planning to conduct fits in the description of the trial that is controlled by the Act, then the investigators should submit the protocol to the Central Drug Standardization Organization (https://www.cdscoonline.gov.in/CDSCO/homepage).

These guidelines are also in accordance with Good Clinical Practice (GCP) guidelines for biomedical studies. These guidelines ensure that all clinical trials are based on the principles of the authenticity of data and protection of human rights of the study participants. The GCP guidelines cover various aspects: (1) Role of the investigators, (2) role of sponsors, (3) design of trials, (4) conducting the trial, (5) communication with the Ethics Committees/Institutional Review Boards, (6) information to the participants and consent procedures, (7) records of trials, (8) progress reports, (9) safety and adverse event reports, (10) termination of the trials, and (11) final report.

Although we have described some common topics covered under these guidelines, the list is not exhaustive. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (http://www.ich.org/home.html), the World Health Organization, and the Indian Central Drugs Standard Control Organization have drafted these guidelines. We have provided a link to these documents in the bibliography section; the readers will find these documents useful. In fact, many sponsors and funders require that the investigators should have taken a course on GCP guidelines.

Summary

In an observational study, there is no modification or allocation of the exposure by the researcher. If, however, the researcher allocates or modifies the exposure, then it is called an interventional study. In a clinical trial, study participants are (usually) divided into two groups. One group is then given the intervention and the other group is not given the intervention (or may be given some existing standard of care). The intervention is (usually) assigned randomly. They are then followed over time to assess the change in the outcomes in both the groups. We compare the outcomes in these groups and assess the role of intervention. Some of the analytical methods (such as interim analysis) require extensive statistical consultation; thus, it is important that investigator works closely with statisticians during the design and implementation of RCTs.

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Conflicts of interest

There are no conflicts of interest.

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